



# Cannabis-Based Medicines Palliative Care

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# Who Are Palliative Patients?

Would you be surprised if this patient died in the next 12 months?

Life-limiting illness

- Advance cancers
- Advance diseases with poor prognosis:
  - End-stage heart failure
  - End-stage lung diseases
  - End-stage renal failure
  - End-stage neurological diseases
- Advance dementia
- HIV/AIDS





# Palliative Care

- An approach that improve QOL of patients and family facing life threatening illness
- Prevention and relief of suffering
- Early identification
- Impeccable assessment
- Treatment of pain and other problems
- Psychosocial & spiritual care
- Provided in conjunction with disease specific treatment

# Clinical Interventions Depend on...

- Illness trajectory
- Available therapies
- Patient preference
- Goal of care

## Assessment Needs Encompass a Combination of Clinical Outcomes

- Survival benefit
- Functional goals
- Symptom control
- Psychosocial-spiritual well being



# Symptoms Prevalence in Cancer Patients

- Pain 35 - 96%
- Depression 3 - 77%
- Anxiety 13 - 79%
- Delirium 6 - 93%
- Fatigue 32 - 90%
- Breathlessness 10 - 70%
- Nausea 6 - 68%
- Constipation 23 - 65%
- Anorexia 30 - 92%

# Guiding Principles of Palliative Symptom Management

1. Careful assessment, including pathophysiological cause (s);
2. For first line therapy, consider the number needed to benefit and number needed to harm from most recent evidence;
3. Consider the role of non-pharmacological therapies;
4. Regular assessment of both benefits and harms;

# Guiding Principles of Palliative Symptom Management

5. Aware of off-label and unregistered medicines with appropriate share-decision making and consent from patient;
6. Consider pharmacokinetics (renal failure, hepatic impairment, weight loss);
7. Consider pharmacodynamics (eg. co-existing cognitive impairment);
8. Consider drug-drug interactions (other psychoactive medications eg. opioids, benzodiazepines, antidepressants, and antipsychotics)



# Patients Seek Medicinal Cannabis

- Australian cancer patients 26% reported prior medicinal cannabis use, commonly for pain, appetite loss, insomnia, N/V, psychosocial symptoms
- 1/4 US cancer patients report medicinal cannabinoid use for pain, N/V, appetite loss, stress management, improve mood

# Cannabinoids in Symptom Management

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## Symptoms Responsive to Cannabinoids

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- Depression 3 - 77%
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# Medical Cannabinoids in Cancer Pain & Palliative Care Existing Evidence

## Original Investigation

# Cannabinoids for Medical Use A Systematic Review and Meta-analysis

- 69 RCT, 4 were low risk of bias, 6462 patients
- Most trials showed improvement in symptoms associated with cannabinoids but did not reach statistical significance in all trials.

**CONCLUSIONS AND RELEVANCE** There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

# Systematic review and meta-analysis of cannabinoids in palliative medicine

Martin Mücke<sup>1,2,3\*†</sup>, Megan Weier<sup>4,5†</sup>, Christopher Carter<sup>1†</sup>, Jan Copeland<sup>4</sup>, Louisa Degenhardt<sup>4</sup>, Henning Cuhls<sup>1</sup>, Lukas Radbruch<sup>1,6</sup>, Winfried Häuser<sup>7†</sup> & Rupert Conrad<sup>8†</sup>

- 9 studies with moderate risk of bias, total 1561 participants.
- Participants: Any age, diagnosis of adv/end-stage disease.
- Intervention: Herbal cannabis, syn cannabinoids in every form of application and dose.

## Cancer patients:

- No improvement of: caloric intake, appetite, N/V
- No improvement of pain reduction >30%

## HIV patients:

- Improve weight gain, appetite
- No improvement for N/V
- Megestrol - superior to cannabinoids in improving appetite in cancer and in HIV patients

# Systematic review of systematic reviews for medical cannabinoids

Pain, nausea and vomiting, spasticity, and harms

- 15 RCT – 30% pain reduction: RR 1.37 (95%CI 1.14-1.64), NNT = 11.
- 4 RCT – positive global impression of change in spasticity RR 1.45 (95%CI 1.08-1.95), NNT = 7.
- 7 RCT – N/V after CMT RR 3.60 (95%CI 2.55-5.09), NNT = 3.
- Adverse effects: dizziness NNH = 5, sedation NNH = 5, confusion NNH = 15, dissociation NNH = 20.
- “Feeling high” 35-70%



# Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

- 750 publications identified,  
11 SRs met the inclusion criteria;  
3 of them were of high and  
8 of moderate methodological quality,  
2 prospective long-term observational studies
- Medical cannabis and 1 with THC/CBD spray  
were also analyzed.

# Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

## Neuropathic pain

- 3 SRs (25 RCTs, 1837 patients) study duration 5h-15wk.
- Pain relief of  $\geq 30\%$  NNT 6; NNH 25.
  - Cannabinoids can be used as 3<sup>rd</sup> therapy in careful selected patients.

## Cancer pain

- 2 SRs (2 RCTs, 307 patients) study duration 2 & 3 wks.
- Pain relief  $>30\%$  were just above threshold.
- No significant differences in tolerability.
  - Limited data available for use in cancer pain.

# Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

## Pain Management

- Limited evidence for a benefit of THC/CBD spray in the treatment of neuropathic pain.
- Inadequate evidence benefit of cannabinoids (dronabinol, nabilone, medical cannabis, or THC/CBD spray) to treat cancer pain, pain of rheumatic/GI origin/anorexia in cancer or AIDS.
- Treatment with cannabis-based medicines is associated with CNS and psychiatric side effects.

# Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

**Appetite, weight and N/V in advance diseases**

**HIV/AIDS.**

- 2 SRs, 6 RCTs, 350 HIV/AIDS patients, duration of study 3 and 12wks.
- No statistic significant differences.
  - Insufficient evidence was available to support the use in treating loss of appetite, nausea and weight loss

# Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

## Appetite, weight and N/V in advance diseases Cancer

- 1 SR, 3 RCTs, 441 cancer patients,
- No statistical significant differences  
→ Insufficient evidence

## Alzheimer disease

- 2 SRs, 1 RCT, 15 Alzheimer patients, duration 12 wks.  
→ No evidence recommendation

# Cannabinoids in Pain Management and Palliative Medicine

An Overview of Systematic Reviews and Prospective Observational Studies

## Prospective long-term observational studies

- 3 studies, 439 patients, study duration 38 wks.
- Half of patients report pain relief of >30%, 1/3 had pain relief of >50%.
- 23% discontinued due to AEs, 11% severe AEs



## Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer

Lihi Bar-Lev Schleider<sup>a,b</sup>, Raphael Mechoulam<sup>c</sup>, Violeta Lederman<sup>b</sup>, Mario Hilou<sup>b</sup>, Ori Lencovsky<sup>a</sup>, Oded Betzalel<sup>b</sup>, Liat Shbiro<sup>a</sup>, Victor Novack<sup>a,\*</sup>

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<sup>b</sup> Research Department, Tikun Olam LTD, Israel

<sup>c</sup> Institute for Drug Research, School of Pharmacy, the Hebrew University of Jerusalem, Israel

- 2,970 patients, different types of CA, 51% stage 4
- Av age 59.5+16.3y
- Reviewed data (questionnaires): baseline, 1 and 6 M.
- Main symptoms: sleep problems (78.4%), pain (77.7%), weakness (72.7%), nausea (64.6%) lack of appetite 48.9%)

- After 6 M. 24.9% died, 18.8% stopped treatment.
- Of the remaining 1211 (60,6%) responded
  - 95.9% reported improvement in their condition
  - 3.7% no change
  - 0.3% deterioration in their med condition.

Due to the observational nature of the study → **No causality between cannabis therapy and symptom improvement can be established.**

- Pain intensity: initial reported as very high in 50%
- After 6m. → <5%
- Decreased in opioids use
  - 36% stopped taking opioids
  - 9.9% decreased the dose.

# Symptom Areas with Potential Role for Cannabinoids in Palliative Care

## Nausea:

- Often multifactorial causes
- Treatment needs to consider reversible causes
- First line drugs: prokinetic agents, dopamine receptor antagonist
- Cannabinoids studies were mostly in CINV

**Insufficient data to draw conclusion**

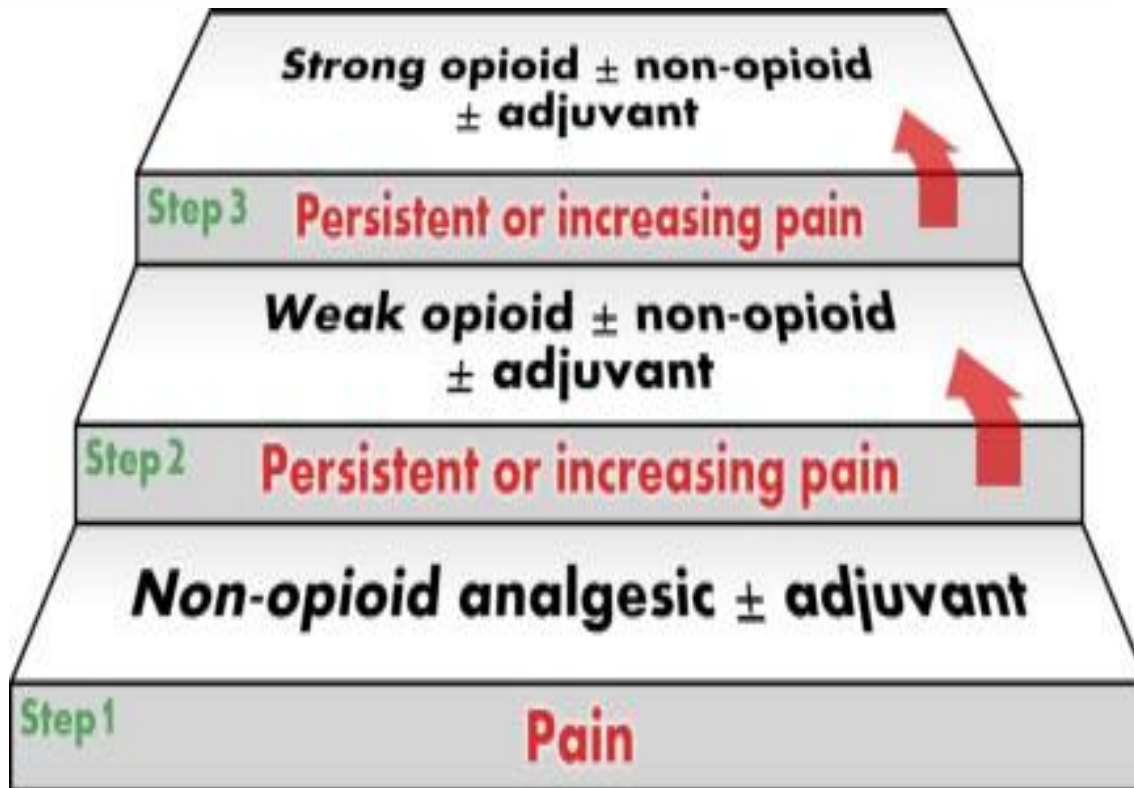
# Symptom Areas with Potential Role for Cannabinoids in Palliative Care

## Cancer pain

- Preclinical data supports the potential role of cannabinoids in pain modulation
- Clinical evidence to date - still not support
- 3 recent phase 3 studies of nabiximols in advance cancer with pain that is unrelieved despite optimized opioids failed to demonstrate benefit

# Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

*Lancet Oncol 2012; 13: e58–68*



Low doses of step III opioid may be used instead of codiene or tramadol (Step II)

# Symptom Areas with Potential Role for Cannabinoids in Palliative Care

## Anorexia

- Current pharmacological therapies for anorexia: Progestin, corticosteroids provide limited and short-term improvement, limited by SE.
- THC has effects in the hypothalamus and on dopamine transmission → benefit effects
- Study on HIV-AIDS no benefit, but short duration, in small numbers of patients
- Two phase 2 studies – impact on appetite and improved food taste in cancer patients.
- Three phase 3 studies failed to show benefits

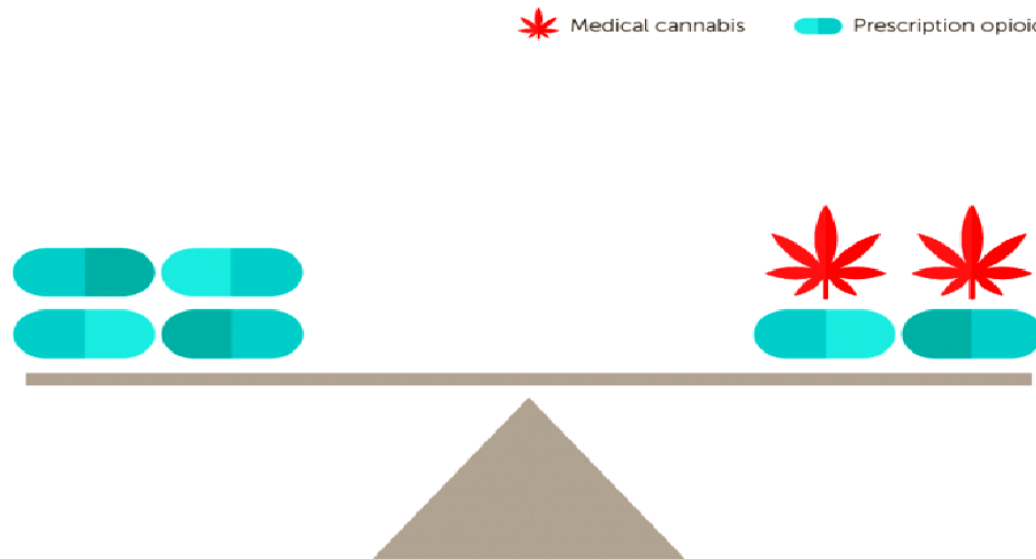
*Lutge EE, et al. Cochrane Database Syst Rev 2013; CD005175.*  
*Nelson K, et al. J Palliat Care 1994;10:14-8.*  
*Jatoi A, et al. J Clin Oncol 2002;20:567-73.*  
*Strasser F, et al. J Clin Oncol 2006;24:3394-400.*



# Opioid-Cannabinoid Combination for Pain?

Medical Cannabis Can Allow Pain Patients  
To Take Lower Doses Of Opioids

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- CB1 receptors and opioid receptors ( $\mu$ -opioid receptor) are found in spinal cord, periaqueductal area, basing reward center.
- Once activated by either receptors → share common signal

# Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

Kevin F. Boehnke<sup>□</sup>, Evangelos Litinas<sup>†</sup>, Daniel J. Clauw<sup>‡,§,□,✉</sup>

Cross-sectional retrospective survey in patients with chronic pain

- Cannabis use was associated with a 64% decrease in opioid use (n=118)
- Decreased number and side effects of medications, and improved QOL 45%



ARTICLE

# Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability

Ziva D. Cooper<sup>1</sup>, Gillinder Bedi<sup>2</sup>, Divya Ramesh<sup>3</sup>, Rebecca Balter<sup>1</sup>, Sandra D. Comer<sup>1</sup> and Margaret Haney<sup>1</sup>

- Double-blind, placebo-controlled trial study the effects of low dose cannabis (5.6% THC) and oxycodone 2.5mg on pain threshold in human subjects
- Neither cannabis nor oxycodone independently effect pain, but when used in combination → increased threshold to pain stimuli

# Other Potential Benefits in Pain Management

- Preclinical data suggesting that cannabinoids may have a role in reversing opioid-associated hyperalgesia
- Cannabinoids may reduce craving and relapse risk in opioid dependency
- Prevent or treat CMT-induced peripheral neuropathic pain

*Cichweicz DL, et al. J Pharmacol Exp Therap 2003;304:1010-14.*

*Hurd YL. Trends Neurosci 2017;40:124-7.*

*Lynch ME, et al. J Pain Symptom Manag 2014;47:166-72.*

# Model Development Recommended: Medical Cannabinoids in Pain & PC

- Opioids are the main drugs used in pain control in palliative patients.
- Use only medicinal cannabis.
- Evidence-based recommendations for applications in specific symptoms, which failed 2-3<sup>rd</sup> line therapy. (Cancer pain, neuropathic pain, CINV, spasticity)

# Model Development Recommended: Medical Cannabinoids in Pain & PC

- In end-of-life phase (<3months), mild euphoria, sense of well being, heighten of sensory perception from cannabis may play a role in psychological/spiritual suffering.
- Cannabis may be superior to unknown herbal drugs, which many palliative patients used and may cause serious side effects.



# Cannabis and Quality of Life



# Quality of Life

- QoL composed of physical, psychosocial and spiritual aspects
- Gold standard - self report
- The most important outcome in palliative care

# How to Measure QOL in Palliative Patients

- QOL assessment needs to include spiritual well being
- Most QOL questionnaires for cancer lack spiritual assessment
- In dying patients this domain is sometime override physical domain

# Cannabis for Psychosocial and Spiritual Wellbeing?

- Effects of mild euphoria and sense of well being may impact on existential and spiritual wellbeing
- Cannabis not only relief of physical symptoms, but also enhance wellbeing and restore a sense of normalcy through euphoria and enhanced sensorium and awareness





The Vedas refer to it as a  
"source of happiness", "joy-giver" and "liberator"

# Cannabis and Quality of Life

- Patients with head and neck CA better tolerated RT when they used cannabis

*(Elliott DA, et al,. Support Care Cancer 2016;24:3517-24)*

- Cannabis lowering the amount of prescription drugs patients required

*(Corroon JM, et al. J Pain Res 2017;10:989-98.)*

- Study of 184 patients with chronic pain
  - Reduction in use of opioids (119 → 33)
  - Non-steroid pain killers (115 → 38)
  - Anti-rheumatic drugs, antidepressants

*(Boehnke KF, et al. J Pain 2016;17:739-44)*

# Cannabis and Quality of Life

- Meta-analysis – articles assessing HRQOL during treatment with cannabis and cannabinoids (20 articles met quality criteria)
- Results - contradictory
- Most consistently positive results were in patients with chronic pain
- Improvement in HRQOL among patients who used herbal cannabis as compared to those using pure cannabinoids



# Cannabis and Quality of Life

- Reduction in the number of deaths from opioids overdose in the last 10 years as compared to US states with no such legislation

*(Bachhuber MA, et al. JAMA Intern Med 2014;174:1668-73.)*

- Retrospective review on death certificate data, opioid overdose deaths in patients with cancer is very small

*(Chino F. 2018 ASCO Quality Care Symposium. Abstract 230.)*

# Safety Issues

- Young people
- Preexisting (particularly psychosis) mental illness
- Existing substance abuse problems.

- Regular cannabis use can unmask or hasten the onset of psychotic illness
- Associated with reduced IQ
- Addiction/dependence, withdrawal syndrome.
- Dropping out of school, decreased motivation, socialization, and life-satisfaction
- Chronic bronchitis.

# Safety Issues

- Significant trends toward decreases in opioid overdose deaths in states with legalized cannabis
- Fewer overall traffic deaths after legalization
- Reductions in pre-versus-post legalization Medicare expenditures on prescription analgesics, sedative-hypnotics, anxiolytics, and other agents.



Australian Government

Department of Health

Therapeutic Goods Administration

Guidance  
for the use of  
**medicinal cannabis**  
in the treatment of  
**palliative care**  
**patients**  
in Australia

Version 1, December 2017

# Limitations

- GL only relate recommendations to the condition, drug and dose which have been studied.
- Limitations in how the evidence was obtained and reviewed.
- Dose-response information for efficacy is lacking, in particular for starting doses, particularly relevant when applying data from young people to the frail elderly or people with cachexia, cognitive impairment and hepatic or renal disease.

# Limitations

- Dose-response information for toxicity is also lacking, particularly side effects which may overlap with symptoms of distress.
- Side effects may occur at varying doses in this population and before efficacy is evident. Side effects which are reversible in young people on ceasing the medicinal cannabis product may not be irreversible in this setting.
- No dose equivalent safety or efficacy data between specific medicinal cannabis products and current best practice

# Recommendations

- Strongly recommended that doctors emphasize the **limited evidence for medicinal cannabis and the possibility of adverse events.**
- **The absence of evidence for first-line or sole use of cannabinoid products in PC.**
- Used after standard palliative treatment have been considered and used



# Recommended Duration of Medication Trial

- Little evidence based on the studies identified in the systematic review to inform decisions about treatment discontinuation.
- Rule of thumb – **discontinued if no benefits have been detected (4-12 wks).**

## Adverse Effects

- Sedation, nausea and dizziness are report commonly.
- Serious AE: psychosis, cognitive distortion.

## Key to grades

- A** Strong scientific evidence for this use
- B** Good scientific evidence for this use
- C** Unclear scientific evidence for this use
- D** Fair scientific evidence against this use (it may not work)
- F** Strong scientific evidence against this use (it likely does not work)

## Alzheimer's disease

Evidence Grade	Cannabinoid used	Outcomes
C	Dronabinol	<u>Weight gain occurred in both treatment phases</u> but patients who received cannabinoids before placebo gained more weight than patients who received placebo first.
C	Dronabinol	<u>Negative affect decreased in both therapy phases</u> but significantly greater reductions were observed when patients were receiving cannabinoids.

# Symptom Control in Cancer

Evidence Grade	Cannabinoid used	Outcomes
C	Dronabinol, THC:CBD, THC	There was a <u>non-significant effect of medicinal cannabis to reduce cancer pain.</u>
D	Dronabinol, THC:CBD, THC	There were <u>no significant differences between medicinal cannabis and placebo in effects on patients' weight, caloric intake, appetite, nausea and vomiting, sleep, depressed mood, or quality of life.</u> There were also no significant differences between medicinal cannabis and placebo in development of cognitive impairment or dizziness during treatment.

# Symptom Control in Cancer

C	Cannabis sativa	All cancer and anti-cancer treatment symptoms (e.g. nausea, vomiting, mood disorders, fatigue, weight loss) were improved <u>after initiating cannabis therapy</u> . The lack of controlled studies restricts the conclusiveness of this finding and the clinical relevance is also unknown.
C	Dronabinol	Patients receiving dronabinol reported an <u>increase in appetite</u> and a decrease in nausea, however the treatment effects decreased as the disease progressed. The <u>lack of controlled studies</u> restricts the conclusiveness of this finding.
C	Nabilone	Patients receiving nabilone reported <u>decreases in pain scores, morphine use, nausea, anxiety, overall distress, and borderline significant improvement in appetite</u> . The <u>lack of controlled studies</u> restricts the conclusiveness of this finding.

# Summary

- Reasonable evidence that cannabinoids can help with some forms of chronic pain, CINV, MS-related spasticity, and central pain.
- FDA-approved pharmaceutical cannabinoids may worth of clinical trial in patients with difficult to manage symptoms
- Considerable uncertainty about the chemical composition and purity of dispensary product
- Patient counseling on known risks, inadvertent exposure of others, safe storage, risk of fall, etc.
- Physician should familiarize with clinical picture of intoxication, abuse, dependency, and withdrawal states.





**Affirms life**

**Promotes quality of life**

**Treats the person**

**Supports the family**